REMARKS

Reconsideration and withdrawal of the Examiner's rejections are requested respectfully.

Status of the Claims

Claim 24 has been amended to include the recitations of dependent Claims 41 to 44. Claim 47 has been amended to include the recitations of Claim 52 and Claim 53, formerly dependent from Claim 52, has been amended to depend from Claim 47. Claim 42 has been amended to correct a typographical error. Claim 52 has been cancelled without prejudice. Claim 54 has been added. Support for Claim 54 is found in Claim 1 as filed originally. The Claims pending presently are Claims 1 to 5, 20 to 51, 53 and 54.

Discussion of Applicants' Invention

Applicants have developed a coated multiparticulate formulation for the extended delivery of an SSRI or a pharmaceutically acceptable salt thereof. The period of release of the SSRI is over a period of not less than about 12 hours following oral administration. The extended-release properties of the formulation is a function of a rate-controlling polymer coating on the particles of the multiparticulate formulation. Further, as the different SSRIs have different properties (e.g., different structures, different molecular weights), it is intuitive that the release properties of the formulation is dependent also upon the particular active agent used.

Discussion of the Art Cited

European Patent No. 0 797 991 to American Home Products

The '991 patent discloses coated multiparticulate formulations for delivery of venlaflaxine-HCl over an extended period. Venlaflaxine-HCl is an antidepressant but is not an SSRI. The patent, however, does not disclose any formulation comprising an SSRI.

U.S. Patent No. 5,958,458 to Norling et al.

The '458 patent discloses coated multiparticulate formulations for delivery of an active agent. The coating may be formulated for extended release, delayed release, or modified release of the active agent. The patent discloses that antidepressants such as imipramine, nortriptyline, and pritiptylene (none of which are an SSRI) may be used as the active agent in the formulations described therein but does not disclose the use of any any specific formulation comprising any antidepressant, let alone one comprising an SSRI.

U.S. Patent No. 4,851,228 to Zentner et al.

The '228 patent discloses coated multiparticulate formulations for delivery of an active agent. Release of the active agent is dependent upon the osmotic gradient between the particles and the environment. The patent discloses that antidepressants such as fluvoxamine may be used as the active agent in the formulations described therein but does not disclose the use of any specific formulation comprising an SSRI.

U.S. Patent No. 6,183,780 to Van Balken et al.

The '780 patent discloses coated multiparticulate formulations for the delayed immediate release of an active agent. Delayed immediate release is accomplished through the use of a coating which ruptures over time, resulting in an immediate release of the active agent. This contrasts with extended release formulations of the present invention which release the active agent over an extended period of time. The patent discloses that antidepressants such as fluvoxamine may be used as the active agent in the formulations described therein but does not disclose the use of any specific formulation comprising an SSRI.

Discussion of Examiner's § 102(b) Rejection of
Claims 24 and 45 as Being Anticipated by European Patent No. 0 797 991

The Examiner rejected Claim 24, directed to a multiparticulate controlled-release SSRI formulation, and Claim 45, directed to a method for using the same, as being anticipated under Section 102(b) by European Patent No. 0 797 991.

This rejection has been rendered moot by the above amendment to Claim 24, of which Claim 45 includes the recitations thereof. Claim 24 now recites that the formulation defined therein must comprise fluoxetine, fluvoxamine, paroxetine, or sertraline, or a pharmaceutically acceptable salt thereof. The '991 patent does not disclose any such formulations.

Applicants note that the recitations added to Claim 24 are those present in Claims 41 to 44 which have not been subject to the present rejection.

Given the above, applicants request respectfully that the Examiner's rejection

of Claims 24 and 45 as being anticipated by European Patent No. 0 797 991 be withdrawn.

Discussion of Examiner's § 102(e) Rejection of
Claims 24 and 45 to 51 as Being Anticipated by U.S. Patent No. 5,958,458

The Examiner rejected Claims 24 and 46 to 51, directed to a multiparticulate controlled-release SSRI formulation, and Claim 45, directed to a method for using the same, as being anticipated under Section 102(e) by U.S. Patent No. 5,958,458.

This rejection has been rendered moot by the above amendment to Claim 24, of which Claim 45 includes the recitations thereof, and Claim 47, on which Claims 48 to 51 depend. Claim 24 now recites that the formulation defined therein must comprise fluoxetine, fluvoxamine, paroxetine, or sertraline, or a pharmaceutically acceptable salt thereof. The '458 patent does not disclose any such formulations.

Applicants note that the recitations added to Claim 24 are those present in Claims 41 to 44 which have not been subject to the present rejection. The recitations added to Claim 47 are those present in now cancelled Claim 52 which has also not been subject to the present rejection.

Given the above, applicants request respectfully that the Examiner's rejection of Claims 24 and 45 to 51 as being anticipated by U.S. Patent No. 5,958,458 be withdrawn.

Discussion of Examiner's § 103(a) Rejection
of Claims 1 to 5, 20, and 22 to 45 as Being Rendered Obvious
Over European Patent No. 0 797 991 in view of U.S. Patent No. 4,851,228

The Examiner rejected Claims 1 to 5, 20, and 22 to 33, 35 to 44, directed to a multiparticulate controlled-release SSRI formulation, and Claims 34 and 45, directed to a method for using the same, as being rendered obvious by the disclosure of European Patent No. 0 797 991 in view of U.S. Patent No. 4,851,228. According to the Examiner, the '991 patent discloses coated multiparticulate formulations for the extended delivery of an antidepressant, but not the SSRIs recited by the claims. While the '991 patent does not disclose that the formulations therein exhibit the release profile specified by the claims, the Examiner claims that such is inherent unless proven otherwise. According also to the Examiner, the '228 patent discloses coated multiparticulate formulations for the controlled delivery of fluvoxamine. The Examiner has taken the position that one skilled in the art, desiring to make a formulation for the controlled release of fluvoxamine, would have applied the teaching of the '228 patent that fluvoxamine may be used in a controlled release multiparticulate formulation with the disclosure in the '991 patent of a coated multiparticulate formulation which the Examiner claims exhibits the release profile specified by the present claims to arrive at applicants' invention.

The Examiner's rejection is traversed respectfully. To establish a *prima facie* case of obviousness, the Examiner must show: (A) that there is some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the teachings thereof; (B) there is a reasonable expectation of success; and (C) the combined references teach or suggest all the claim limitations. MPEP §2143. Even if we assume the Examiner's premise that the formulations of the '991 patent inherently

have the release profile recited by the claims, the Examiner must still show (A) and (B). The Examiner, however, has failed to do so.

The Examiner's rejection may be traversed on her failure to satisfy the reasonable expectation of success requirement. This is because the '991 patent discloses only venlaflaxine HCl-containing formulations and fluvoxamine is a completely different compound with a different structure. Venlaflaxine has two rings, a benzene ring and a cyclohexyl ring whereas fluvoxamine has simply one ring, a benzene ring. Venlaflaxine has a formula of $C_{17}H_{27}NO_2$ and has a molecular weight of 277.4. Fluvoxamine has a formula of $C_{15}H_{21}F_3N_2O_2$ and has a molecular weight of 318.34. Furthermore, as discussed below, venlaflaxine-HCl is not an SSRI while fluvoxamine is. Accordingly, even if the formulation of the '991 patent would exhibit the recited release profile of the present claims with regard to venlaflaxine-HCl, one skilled in the art would not have had any reasonable expectation that fluvoxamine, substituted for venlaflaxine-HCl in such a formulation would also exhibit such a release profile or that it could even be released from the formulation at all.

If the Examiner persists in her rejection, she is requested respectfully to show how each of the requirements above for a *prima facie* case of obviousness are met. Unless she does so, applicants request respectfully the withdrawal of the present rejection.

Discussion of Examiner's § 103(a) Rejection
of Claims 1 to 5, 20, and 22 to 45 as Being Rendered Obvious
Over European Patent No. 0 797 991 in view of U.S. Patent No. 6,183,780

The Examiner rejected Claims 1 to 5, 20, and 22 to 33, 35 to 44, directed to a multiparticulate extended-release SSRI formulation, Claims 34 and 45, directed to a

method for using the same, as being rendered obvious by the disclosure of European Patent No. 0 797 991 in view of U.S. Patent No. 6,183,780. The '991 patent is being cited for the same reasons as above. The Examiner cites the '780 patent as disclosing coated multiparticulate formulations for the extended release delivery of fluvoxamine. The Examiner has taken the position that one skilled in the art, desiring to make a formulation for the extended release delivery of fluvoxamine, would have applied the teaching of the '780 patent that fluvoxamine may be used in an extended release multiparticulate formulation with the disclosure in the '991 patent of a coated multiparticulate formulation which the Examiner claims exhibits the release profile specified by the present claims to arrive at applicants' invention.

The Examiner's rejection is traversed respectfully. To establish a *prima facie* case of obviousness, the Examiner must show: (A) that there is some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the teachings thereof; (B) there is a reasonable expectation of success; and (C) the combined references teach or suggest all the claim limitations. MPEP §2143. Even if we assume the Examiner's premise that the formulations of the '991 patent inherently have the release profile recited by the claims, the Examiner must still show (A) and (B).

The Examiner's rejection may be traversed on her failure to show that there is some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the teachings thereof. In the first instance, it should be pointed out that the Examiner is incorrect in stating that the '780 patent discloses a formulation for the extended release of fluvoxamine. The '780 patent does not disclose specifically any fluvoxamine-containing formulation and merely lists fluvoxamine as a potential active

agent for use in the formulations disclosed therein. More importantly, the '780 patent does not disclose any extended release formulation at all. As stated above, the '780 patent discloses only delayed immediate release formulations. These are not formulations for allowing the controlled release of an active agent over a period of not less than about 12 hours, as specified by the claims. Rather, after a period of time in which no or little active agent is released, the active agent is suddenly released with no control at all. Therefore, even if the Examiner takes the position that the '780 patent suggests the use of fluvoxamine in the formulations disclosed therein, it still does not suggest that fluvoxamine may be used in an extended release formulation as claimed by the Examiner. As such, one skilled in the art would not have been motivated to combine the teaching of the '780 patent, which relates to a delayed immediate release formulation, with that of the '991 patent, which relates to an extended release formulation, as the two references relate to completely different formulations.

The Examiner's rejection may be traversed also on her failure to satisfy the reasonable expectation of success requirement. This is for two reasons. The first is aforementioned reason that fluvoxamine is different from venlaflaxine-HCl and, therefore, the success of the formulation of the '991 patent in allowing for the specified extended release profile of the claims for venlaflaxine-HCl (assuming that the formulation does exhibit such a profile) does not predict the same success for fluvoxamine. The second reason is that the '780 patent discloses only delayed immediate release formulations and thus even if such formulations would be successful for fluvoxamine, there is nothing in the cited art that shows that fluvoxamine may be successfully employed in an extended release formulation such as the one disclosed by the '991 patent.

If the Examiner persists in her rejection, she is requested respectfully to show how each of the requirements above for a *prima facie* case of obviousness are met. Unless she does so, applicants request respectfully the withdrawal of the present rejection.

Discussion of Examiner's § 103(a) Rejection
of Claims 1 to 5, 20, and 22 to 45 as Being Rendered
Obvious Over U.S. Patent No. 5,958,458 in view of U.S. Patent No. 6,183,780

The Examiner rejected Claims 1 to 5, 20, and 22 to 33, 35 to 44, directed to a multiparticulate controlled-release SSRI formulation, Claims 34 and 45, directed to a method for using the same, as being rendered obvious by the disclosure of U.S. Patent No. 5,958,458 in view of U.S. Patent No. 6,183,780. The Examiner is of the opinion that, as the formulation of the '458 patent contain particles coated in a similar fashion to that of the particles of the claimed formulation, such a formulation inherently possesses the same release profile as that recited by the claims. The '458 does not disclose the use of any of the SSRIs recited by the present claims. The Examiner cites the '780 patent as disclosing coated multiparticulate formulations for the extended release delivery of fluvoxamine. The Examiner has taken the position that one skilled in the art, desiring to make a formulation for the extended release delivery of fluvoxamine, would have applied the teaching of the '780 patent that fluvoxamine may be used in an extended release multiparticulate formulation with the disclosure in the '458 patent of a coated multiparticulate formulation which the Examiner claims exhibits the release profile specified by the present claims to arrive at applicants' invention.

The Examiner's rejection is traversed respectfully. To establish a *prima facie* case of obviousness, the Examiner must show: (A) that there is some suggestion or

motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the teachings thereof; (B) there is a reasonable expectation of success; and (C) the combined references teach or suggest all the claim limitations. MPEP §2143. Even if we assume the Examiner's premise that the formulations of the '458 patent inherently have the release profile recited by the claims, the Examiner must still show (A) and (B).

The Examiner's rejection may be traversed on her failure to show that there is some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the teachings thereof. As stated above, the Examiner is incorrect in stating that the '780 patent discloses a formulation for the extended release of fluvoxamine. The '780 patent does not disclose specifically any fluvoxamine-containing formulation and merely lists fluvoxamine as a potential active agent for use in the formulations disclosed therein. More importantly, the '780 patent does not disclose any extended release formulation at all. Rather, the '780 patent discloses only delayed immediate release formulations. These are not formulations for allowing the controlled release of an active agent over a period of not less than about 12 hours, as specified by the claims. Rather, after a period of time in which no active agent is released, the active agent is suddenly released with no control at all. Therefore, even if the Examiner takes the position that the '780 patent suggests the use of fluvoxamine in the formulations disclosed therein, it still does not suggest that fluvoxamine may be used in an extended release formulation as claimed by the Examiner. As such, one skilled in the art would not have been motivated to combine the teaching of the '780 patent, which relates to a delayed immediate release formulation, with that of the '458 patent, which relates in part to an extended release formulation, as the two references relate to completely different formulations.

The Examiner's rejection may be traversed also on her failure to satisfy the reasonable expectation of success requirement. The '780 patent discloses only delayed immediate release formulations and thus even if such formulations would be successful for fluvoxamine, there is nothing in the cited art that shows that fluvoxamine may be successfully employed in an extended release formulation such as the ones disclosed by the '458 patent.

If the Examiner persists in her rejection, she is requested respectfully to show how each of the requirements above for a *prima facie* case of obviousness are met. Unless she does so, applicants request respectfully the withdrawal of the present rejection.

Discussion of the Examiner's Rejection of Claims 23, 24,
and 28 to 30 Under the Enablement Requirement of Section 112, First Paragraph

The Examiner rejected Claims 23, 24, and 28 to 30, each directed to a multiparticulate controlled-release SSRI formulation in which the release of the SSRI exhibits a specific *in vitro* dissolution pattern when measured using a USP type II dissolution apparatus (paddle) according to US Pharmacopeia XXII in 0.05 M phosphate buffer at pH 6.8, as lacking enablement. According to the Examiner, applicants have only demonstrated only that formulations in which Eudragit® is used as the rate-controlling coating polymer at 4, 6, 8, 10, 12, and 15% and the application does not provide enablement for the use of any polymer at any percent amount.

The Examiner's rejection should be traversed because she has failed to show that one skilled in the art, at the time of the application upon reading applicants' disclosure, would not have been able to practice the invention without undue experimentation.

The standard for determining whether a claim is enabled is whether experimentation needed to practice the invention is undue. MPEP §2164.01. In the present case, the application already suggests various polymers for use in forming the rate-controlling coating (see page 13, lines 22 to 25, page 14 (entire page), page 8, lines 19 to 27, page 9 (entire page), page 10, lines 1 to 17, and page 4, lines 6 to 20). In addition, various thicknesses of the coating are suggested (see page 12, lines 24 to 27, and page 13, lines 1 to 8). Accordingly, while the application may not disclose specifically formulations which exhibit the release profile claimed other than those in which Eudragit® is used as the coating polymer, the application provides adequate guidance in that it provides a suggestion of various other polymers which may be used and the thicknesses at which they may be used. Further, the claims define the release rate based on an *in vitro* dissolution pattern as determined using a standard apparatus. Therefore, all one skilled in the art would have to do to determine which of these polymers may be used and in which thickness they may be used to achieve the desired release profile is to test SSRI-containing cores coated with the polymer of interest at the thickness of interest in the apparatus specified by the claims under the conditions specified by the claims to see whether the polymer and the thickness thereof would allow for the desired release profile. Even if such experimentation is considered tedious, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." MPEP §2164.01.

Given the above, it is applicants' position that one skilled in the art would not have to engage in undue experimentation to practice the invention within the scope of the claims. As such, applicants claims are enabled. If the Examiner persists in her rejection of such claims for lack of enablement, applicants request that she show how, after the required consideration of the *In re Wands* factors, she would still consider that one skilled in the art would have to perform undue experimentation to practice the

claimed invention.

Discussion of Claim 54

Claim 54 mirrors the scope of Claim 1 as filed originally. Claim 54 was added because applicants believe that the scope of Claim 1 as filed originally is patentable. This is because none of the art cited anticipates or renders obvious this claim.

Claim 54 relates to a formulation for the extended release of an SSRI. Neither European Patent No. 0 797 991 nor U.S. Patent No. 5,958,458 disclose formulations comprising an SSRI. The '991 patent discloses only formulations comprising venlaflaxine-HCl. Venlaflaxine-HCl is not an SSRI as it inhibits norepinephrine as well as serotonin and is, therefore, not selective for serotonin (see attached excerpt from "Drug Facts and Comparisons 2001", Facts and Comparisons (St. Louis, 2000)). As such, the '991 patent does not anticipate this claim. Applicants note that their Reply of March 11, 2004 erroneously identified venlaflaxine-HCl as an SSRI and referred to areas of the application purportedly naming it as such. This was a clear error as the above facts show that it is not an SSRI and a careful reading of the application shows that venlaflaxine is identified therein only as a potential active agent for use in the formulation of the present invention and not as an SSRI. The '458 patent, as stated above, does not disclose the use of an SSRI either.

With respect to obviousness, applicants submit that the traversal arguments presented above would apply to Claim 54 should such art be used against Claim 54.

Given the above, applicants believe Claim 54 to be allowable. If the Examiner agrees, then applicants plan to present dependent claims therefrom.

Discussion of the Examiner's Election of Species Requirement

Applicants elect the species of the invention in which fluvoxamine or a pharmaceutically acceptable salt thereof is the SSRI as the species to which the claims shall be restricted id no generic claim is finally held to be allowable. Claims 1 to 5, 20, 22 to 40, 42, 45 to 51, and 53 are readable thereon.

Conclusion

For the reasons presented above, it is requested respectfully that the Examiner withdraw her various rejections and objections.

An early and favorable Action is requested respectfully.

Respectfully submitted,

Gene J. Yao, Esquire
Reg. No. 47,193
Attorney for Applicants

Synnestvedt & Lechner LLP
Suite 2600
Aramark Tower
1101 Market Street
Philadelphia, PA 19107-2950
(215) 923-4466

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